CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-986/S-006

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Addendum #1

NDA#: 20-896 SE1-006
Applicant: Hoffmann-LaRoche Inc.
Name of Drug: Xeloda (capecitabine)
Indication: First line treatment of advanced and/or metastatic colorectal cancer
Document Reviewed: Vols. 1-8, dated Oct 30, 2000
Medical Officer: Alison Martin, M.D.

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This review addendum evaluates the impact of age and creatinine clearance on the safety of Xeloda. Three factors, age, Creatinine clearance, and race, were selected in the sponsor's safety analyses. The reason why race was selected in the adjusted analyses is not clear. This reviewer has conducted multivariate Cox regression analysis based on only two factors: age and creatinine clearance. Both variables were categorized, and the cutoffs selected for age were 60 and 80 and the cutoffs for Creatinine clearance were 80, 50, 30. The following tables summarize the Cox regression analyses performed by the FDA on time to adverse events.

Reviewer's Table 1. FDA's Cox Regression Model: **Age cutoff=60,**
Creatinine Clearance cutoffs = 30,50,80
Multivariate Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Age >=60, n=517 < 60, n=358	1.064	.825-1.372	0.635
Creatinine Clearance	0.814	.694-.954	0.011

Reviewer's Table 2. FDA's Cox Regression Model: **Age cutoff=80,**
Creatinine Clearance cutoffs = 30,50,80
Multivariate Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Age >=80, n=21 < 80, n=854	1.805	.975-3.343	0.06
Creatinine Clearance	0.822	.705-.959	0.012

Reviewer's Table 3. FDA's Cox Regression Model: Subgroup Analysis
Creatinine Clearance 50 – 80 vs. >80,
Multivariate Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Age*	1.013	1-1.206	0.053
Creatinine Clearance 50 – 80, n=373 >80, n=397	0.839	.641-1.098	0.201

*Continuous variable.

Summary and Conclusion:

The FDA's analyses show that creatinine clearance has additional statistically significant impact on the safety of Xeloda (Reviewers Tables 1 and 2). Age also has the impact on the safety profile. Particularly, for those patients older than 80 years, there may be some serious safety concerns . The result in Tale 2 shows that patients older than 80 years may have 80% higher risk of experiencing toxicity than those patients younger than 80 years (after adjusting for creatinine clearance). The marginal significant p-value (p=.06, 95%CI: .975-3.343) may be due to the small sample size in age 80 group (n=21). The result in Table 3 shows that there is no statistically significant difference in safety between patients with Creatinine Clearance 50 – 80 and Creatinine Clearance >80 after adjusting for age.

The result (p-values) of the sponsor's final model (selected model without age, Sponsor's Table 9) is difficult to interpret. The exclusion of age from the full model seems arbitrary and subjective. In the sponsor's full model, race was demonstrated as a factor with the small p-value (p=.03) associated with the safety of Xeloda. The sponsor needs to consult with the FDA medical reviewer whether race is a clinically meaningful factor, and due to the exploratory nature of the Cox regression analyses, the interpretation of the results should be with caution.

/S/ 4/23/01

Gang Chen
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/S/ 4/24/01

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Biostatistician

Statistical Review and Evaluation

NDA#: 20-896 SE1-006

Applicant: Hoffmann-LaRoche Inc.

Name of Drug: Xeloda (capecitabine)

Indication: First line treatment of advanced and/or metastatic colorectal cancer

Document Reviewed: Vols. 1-8, dated Oct 30, 2000

Medical Officer: Alison Martin, M.D.

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Xeloda (capecitabine) supplement NDA20-896 was reviewed on Aug. 30, 2000 and an approvable letter dated September 20, 2000 was sent to the sponsor. In the letter, the FDA requested the sponsor to provide some additional data regarding the renal toxicity and a Phase I, single arm, pharmacokinetic study report (Study WP15811). The sponsor submitted this serial documentation (SE1-006) to fulfill the requirement. The medical and biopharmaceutical reviewer reviewed the submission and requested a statistical consultant on the statistical analysis of a Cox regression model that the sponsor performed in the report.

This reviewer received a data-set from the sponsor dated Nov 6, 2000. The data-set contains 3 relevant variables: time to adverse events, age and creatinine clearance (both are continuous variables). Table 1 and Table 2 summarized the Cox regression analysis performed by this reviewer on the time to adverse events as performed by the sponsor.

Table 1. Cox Regression Model: Univariate Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Age	1.016	1.01-1.03	0.0046
Creatinine Clearance	0.993	0.989-0.998	0.0042

Table 2. Cox Regression Model: Multivariate Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Age	1.012	0.999-1.03	0.0046
Creatinine Clearance	0.996	0.991-1.001	0.0042

Comment:

The FDA's results are consistent with the sponsor's reported results. The implication of the results should be based upon clinical and PK/PD judgement.

/S/ 2/5/01

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Biostatistician

Concur:

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Pelosi

JUL 10 2000

Statistical Review and Evaluation
Review of Carcinogenicity Data

NDA Number:	20-896, Animal Carcinogenicity Studies
Applicant:	Hoffmann-La Roche
Drug Name:	Xeloda (Ro 09-1978)
Indication:	Colorectal cancer
Document reviewed:	Supplemental NDA submission. Volumes 11-18.
Date of submission:	February 25, 2000
Pharmacology Reviewer:	William McGuinn, Ph. D. (HFD-150)
Statistical Reviewer:	John Lawrence, Ph. D. (HFD-710)

1. Introduction

A 24-month oral (feed admix) carcinogenecity study was conducted in BDF1 mice to assess the carcinogenecity potential of Ro 09-1978/000, a tumor selective anti-tumor drug. Mice were randomly divided into five groups stratifying by gender (50 males and 50 females per group) – two controls and three separated dosage level groups (30, 60 and 90 mg/kg/day). Since the two control groups are theoretically identical, the analyses were performed with each control group separately and for the combined control group. All analyses were performed separately by gender. After the 24-month treatment period, all surviving mice were sacrificed and various hematological and pathological examinations were performed.

2. Applicant's Findings

For survival, there were no statistically significant pairwise differences ($p > 0.05$) between any groups of male or female mice and there was no significant increase or decrease in survival rate for increasing dose.

For the tumor findings, as compared to separate control groups, there were no statistically significant trends ($p < 0.01$ and $p < 0.05$ for common and rare tumors, respectively).

In male mice at the low dose, there was a statistically significant increase in the hepatocellular adenoma incidence ($p = 0.0046$; pairwise comparison). The combined hepatocellular adenoma and/or carcinoma incidence was not statistically significant ($p = 0.0137$). Moreover, since there was no increase in hepatocellular tumor incidence at higher doses, this increase was considered incidental and not related to treatment.

For male mice (compared to the controls), there was a tendency for a decrease in the combined bronchioloalveolar adenoma and/or carcinoma incidence with a statistically significant decrease in high dose male mice by pairwise comparison ($p = 0.0099$). For female mice, the histiocytic sarcomas tended to be reduces in all dose groups with a statistically significant decrease in high dose females ($p = 0.0071$) by pairwise comparison.

The sponsor concludes that there was no treatment effect on survival or increased tumor incidence (and thus, no evidence of carcinogenic potential with Ro 09-1978/000 in mice treated at dose levels of up to 90 mg/kg/day for 24 months).

3. Reviewer's Analysis

The number of mice in each group who died in different time intervals appears in Table 3.1. The Kaplan-Meier estimates of the survival curve appear in Figures 3.1a and 3.1b. Both Table 3.1 and Figure 3.1 show no trend toward longer survival among the dose groups.

The p-values from the dose-mortality trend tests appear in Table 3.2. The results of these tests confirm what is visually apparent from the Kaplan-Meier curves and the number of deaths per time interval. None of the p-values for male or female mice are significant.

The entire table of comparisons of organ specific tumors appears in the appendix. In males and females, there is no significant difference for any site.

Table 3.1 Number of deaths per treatment group in different time intervals.

Week	Group				
	Control	30 mg	60 mg	90 mg	Total
[redacted]					
0-52	3	2	0	0	5
53-78	3	1	0	1	5
79-91	1	0	3	2	6
92-104	4	3	4	0	11
105	89	44	43	47	223
Total	100	50	50	50	250
[redacted]					
0-52	0	1	1	0	2
53-78	9	3	4	1	17
79-91	5	4	8	1	18
92-104	62	30	26	34	152
105	24	12	11	14	61
Total	100	50	50	50	250

Figure 3.1a Kaplan-Meier estimates of survival curves for male mice by treatment group.

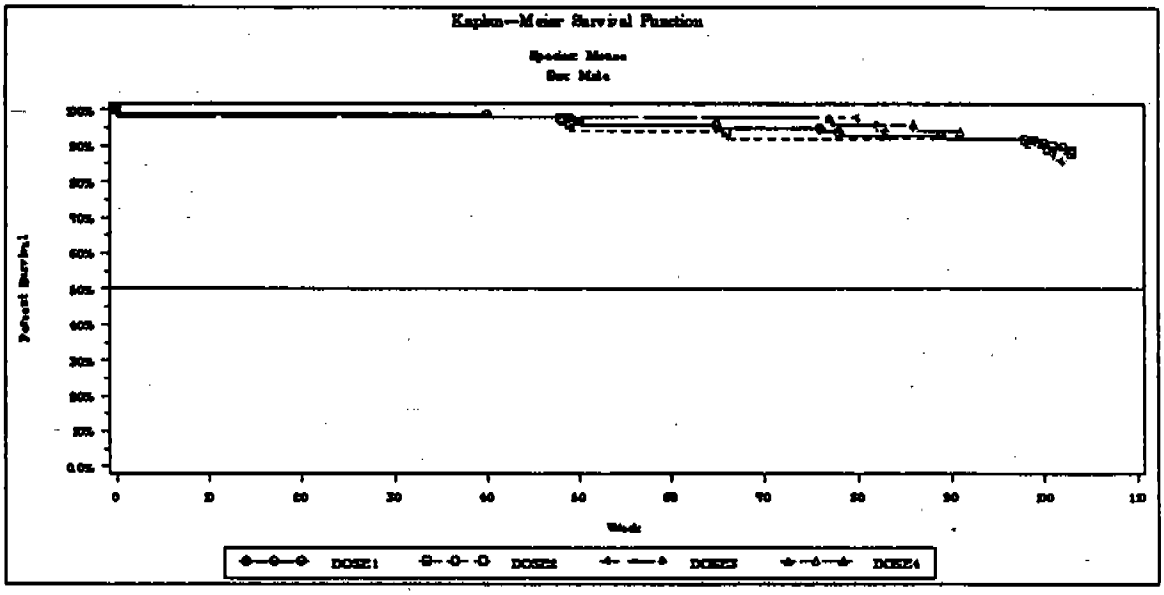

Figure 3.1b Kaplan-Meier estimates of survival curves for female mice by treatment group.

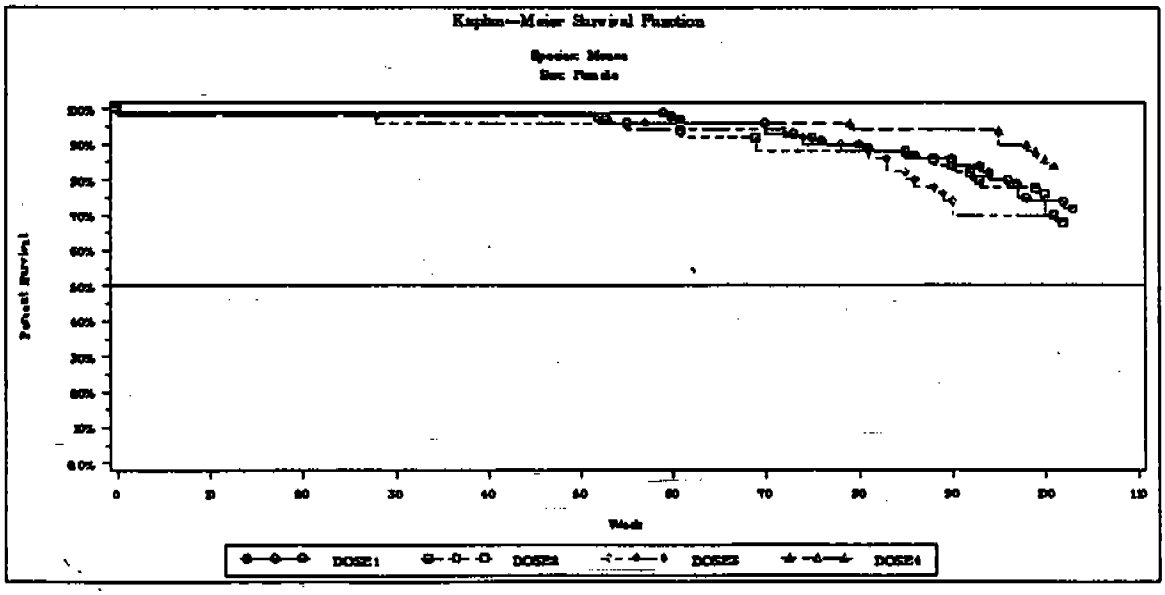

Table 3.2 Dose-Mortality Trend Tests. This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Method	Time-Adjusted Trend Test	Statistic	P-value
Cox	Dose Mortality Trend	0.37	0.5404
	Depart from Trend	1.33	0.5150
	Homogeneity	1.70	0.6365
Kruskal-Wallis	Dose Mortality Trend	0.40	0.5248
	Depart from Trend	1.24	0.5386
	Homogeneity	1.64	0.6499
Cox	Dose Mortality Trend	1.60	0.2059
	Depart from Trend	2.51	0.2858
	Homogeneity	4.11	0.2503
Kruskal-Wallis	Dose Mortality Trend	1.60	0.2055
	Depart from Trend	2.82	0.2440
	Homogeneity	4.42	0.2191

4. Validity of the Mouse Study

There were no statistically significant trends in tumors among the male mice nor among the female mice. Therefore, the validity of the study needs to be evaluated. This requires evidence that enough animals were exposed for a sufficient length of time to allow for late developing tumors and that the dose levels were high enough to pose a reasonable tumor challenge in the animals.

In the highest dose group of males, 47 out of 50 animals survived at least 92 weeks and all of these survived to terminal sacrifice at week 105 (see Table 3.1 of this review). In the highest dose group of females, 48 out of 50 animals survived at least 92 weeks and 14 of these survived to terminal sacrifice. This confirms that there was adequate exposure in the study provided the highest dose is close to the maximum tolerated dose.

The average body weight of surviving male mice at the end of the study was 37.2 g in the control groups and 37.3 g in the highest dose group. For female mice, the average weight in the control groups was 32.0 g and 30.9 g in the highest dose group. If there was a weight loss in the high dose of 10% relative to the control group, then this would provide evidence that the high dose is close to the maximum tolerated dose. However, the amount of weight loss was not 10% in either gender. According to the sponsors summary of the histopathological examinations, there was no evidence of severe histopathological effects attributed to the chemical. No tumor induction and no enhancement of tumor incidence were confirmed and it was concluded that the administered doses have no carcinogenic potential in mice. The apparent observed suppression of tumor development may be ascribed to the antitumor activity of the test article (Study Report, Vol. 11, pp. 18-19). Moreover, the proportion of mice that survived to terminal sacrifice was numerically higher in the high dose than in the control groups. This was true in both genders. Combining all of these observations, there was no evidence from this study that the high dose was close to the maximum tolerated dose.

5. Conclusions

There was no treatment effect observed on survival or increased tumor incidence. However, there is no evidence that the highest dose was near the maximum tolerated dose. Hence, the study may not be valid.

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Appendix

Female Organ Specific Tumor Findings

OrganName	Organ Code	TumorName	Tumor Code	Exact P-Value	Asymp. P-Value
Harderiangland	LG	ADENOMA,ACINARCELL	704	0.2163	0.1805
Harderiangland	LG	CARCINOMA,ACINARCELL	807	1.0000	0.8544
Hemolymphoreticular	HE	LYMPHOMA,MALIGNANT	845	0.7995	0.7809
Hemolymphoreticular	HE	MASTOCYTOMA	753	0.3947	0.2590
Hemolymphoreticular	HE	SARCOMA,HISTIOCYTIC	871	0.9942	0.9923
Largeintestine,colon	CO	LEIOMYOMA	749	1.0000	0.8544
Liver	LI	ADENOMA,HEPATOCELLUL	710	0.5767	0.5157
Liver	LI	CARCINOMA,HEPATOCELL	815	0.7203	0.6716
Liver	LI	HEMANGIOMA	743	0.8184	0.7923
Liver	LI	HEMANGIOSARCOMA	836	0.6978	0.6615
Lung(bronchus)	LU	ADENOMA,BRONCHIOLO-A	705	0.9004	0.8699
Lung(bronchus)	LU	CARCINOMA,ACINARCELL	807	1.0000	0.8544
Lung(bronchus)	LU	CARCINOMA,BRONCHIOLO	806	0.1360	0.1039
Lymphnode	L1	HEMANGIOMA	743	0.7378	0.6252
Mammarygland	MA	ADENOCARCINOMA	801	0.2259	0.1679
Mammarygland	MA	ADENOMA	700	1.0000	0.8496
Ovary	OV	ADENOMA,TUBULAR	714	1.0000	0.8488
Ovary	OV	CYSTADENOMA	727	0.1415	0.1037
Ovary	OV	HEMANGIOMA	743	0.4711	0.3746
Ovary	OV	HEMANGIOSARCOMA	836	1.0000	0.8575
Oviduct	OD	ADENOMA	700	0.4000	0.2664
Pancreas	PC	ADENOMA,ISLETCELL	712	1.0000	0.8544
Pituitary	PI	ADENOMA,ANTERIOR	719	0.7864	0.7563
Pituitary	PI	ADENOMA,INTERMEDIATE	720	0.8340	0.8000
Skeletalmuscle	SU	HEMANGIOMA	743	0.5921	0.5754
Skin	SK	HEMANGIOSARCOMA	836	1.0000	0.9298
Smallintestine,duode	DU	ADENOCARCINOMA	801	0.2323	0.0748
Spleen	SP	HEMANGIOMA	743	0.4098	0.2688
Spleen	SP	HEMANGIOSARCOMA	836	0.9198	0.8847
Sternum	SW	HEMANGIOSARCOMA	836	0.8352	0.8032
Sternum	SW	OSTEOMA	768	0.6066	0.5869
Thyroid	TY	ADENOMA,CCELL	706	0.3947	0.2590
Tibia	TB	OSTEOSARCOMA	860	0.2185	0.0669
Uterus	UT	HEMANGIOMA	743	1.0000	0.8477
Uterus	UT	LEIOMYOMA	749	0.8492	0.8157
Uterus	UT	POLYP,ENDOMETRIALSTR	791	0.5767	0.5157
Uterus	UT	SARCOMA,ENDOMETRIALS	870	0.1672	0.1041
Vagina	VA	POLYP,VAGINALSTROMAL	792	0.6066	0.5869

Male Organ Specific Tumor Findings

OrganName	Organ Code	TumorName	Tumor Code	Exact P-Value	Asymp. P-Value
Adrenal	AD	PHEOCHROMOCYTOMA	773	1.0000	0.8521
Cranialbone	CB	OSTEOMA	768	0.5991	0.5782
Epididymis	EP	HEMANGIOSARCOMA	836	0.4036	0.2573
Femur+marrow	FW	HEMANGIOMA	743	1.0000	0.8521
Femur+marrow	FW	HEMANGIOSARCOMA	836	0.3333	0.1627
Femur+marrow	FW	OSTEOMA	768	0.2108	0.0668
Harderiangland	LG	ADENOMA,ACINARCELL	704	0.1495	0.1212
Heart	HT	HEMANGIOMA	743	1.0000	0.9295
Hemolymphoreticular	HE	LYMPHOMA,MALIGNANT	845	0.6051	0.5721
Hemolymphoreticular	HE	MASTOCYTOMA	753	0.0837	0.0502
Hemolymphoreticular	HE	SARCOMA,HISTIOCYTIC	871	0.6544	0.6211
Kidney	KI	CARCINOMA,TRANSITION	820	0.6009	0.5780
Kidney	KI	PAPILLOMA	770	0.2108	0.0668
Liver	LI	ADENOMA,HEPATOCELLUL	710	0.4981	0.4756
Liver	LI	CARCINOMA,HEPATOCELL	815	0.3300	0.2955
Liver	LI	HEMANGIOMA	743	0.0763	0.0544
Liver	LI	HEMANGIOSARCOMA	836	0.7594	0.7275
Liver	LI	HEPATOBLASTOMA	837	0.6009	0.5780
Lung(bronchus)	LU	ADENOMA,BRONCHIOLO-A	705	0.9760	0.9708
Lung(bronchus)	LU	CARCINOMA,BRONCHIOLO	806	0.8426	0.8152
Lymphnode	L1	HEMANGIOMA	743	0.2447	0.1745
Nasalcavity	NC	SCHWANNOMA,MALIGNANT	874	1.0000	0.8512
Pancreas	PC	ADENOMA,ISLETCELL	712	0.2108	0.0668
Pancreas	PC	HEMANGIOMA	743	0.4036	0.2573
Pituitary	PI	ADENOMA,ANTERIOR	719	0.6836	0.6060
Pituitary	PI	ADENOMA,INTERMEDIATE	720	0.6009	0.5780
Pituitary	PI	CARCINOMA,INTERMEDIA	810	1.0000	0.8540
Skin	SK	HEMANGIOMA	743	1.0000	0.9295
Skin	SK	HEMANGIOSARCOMA	836	0.4100	0.2576
Skin	SK	PAPILLOMA	770	0.6009	0.5780
Skin	SK	TRICHOEPITHELIOMA	799	1.0000	0.8521
Smallintestine,ileum	IL	HEMANGIOSARCOMA	836	1.0000	0.8521
Smallintestine,jejun	JJ	ADENOCARCINOMA	801	0.2453	0.1752
Spleen	SP	HEMANGIOMA	743	0.6009	0.5780
Spleen	SP	HEMANGIOSARCOMA	836	0.5443	0.4850
Sternum	SW	HEMANGIOSARCOMA	836	0.2108	0.0668
Stomach	ST	ADENOCARCINOMA	801	0.2108	0.0668
Testis	TE	LEYDIGCELLTUMOR	746	0.4036	0.2573
Thyroid	TY	CARCINOMA,FOLLICULAR	814	1.0000	0.8513

/S/

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 9 pages of text, tables, and figures.

Concur: Ms. Roswitha Kelly /S/
Dr. Kooros Mahjoob /S/ 07/10/2000

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